

Multiparameter Multiscale Computational Modeling of Tumor Growth and Drug Response

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Dynamic Upscaling and Multiscale Models

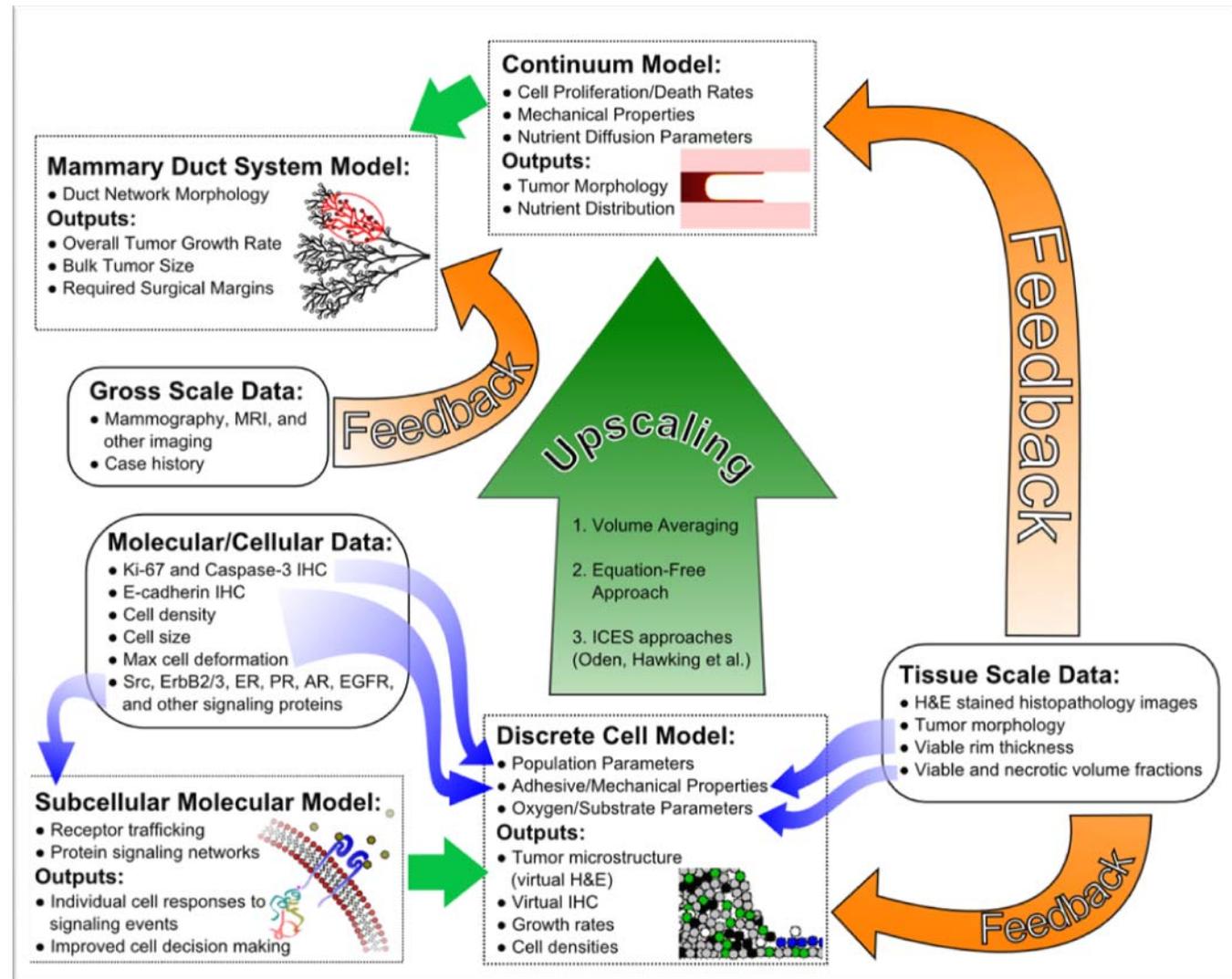
Funding: NSF (math), others

With I Kevrekidis (Princeton) and others

Information flow from data to multiscale model. Tissue-scale (H&E-stained histopathology) and cell/molecular-scale (IHC) data are fed into a *discrete cell model*. The outputs of the cell-scale model are *upscaled* to dynamically calibrate the *continuum tissue-scale model*, leading to predictions at the gross anatomical scale. These results can be compared to known results on patient tumor sizes for further calibration and model refinements.

Biology == emerging behavior

See AACR Math Oncology session, featured *Cancer Res papers*



above: application to breast cancer in collaboration with M Edgerton and others (MD Anderson)

Math/Computational Continuum

Models

Funding: NSF (math), UC Discovery, Orqis Med, others

With J Lowengrub (UC Irvine) and others

V. Cristini, X. Li, J.S. Lowengrub, S.M. Wise, Nonlinear simulations of solid tumor growth using a mixture model: invasion and branching. *J Math Biol.* 2008; DOI 10.1007/s00285-008-0215-x.

→ S M Wise, J Lowengrub, H B Frieboes, V Cristini, Three-dimensional multispecies nonlinear tumor growth--I Model and numerical method. *J Theor Biol*; 253(3):524-43.

V Cristini, HB Frieboes, X Li, JS Lowengrub, P Macklin, S Sanga, SM Wise, X Zheng. Nonlinear modeling and simulation of tumor growth. In: *Selected topics in cancer modeling: Genesis, evolution, immune competition, and therapy*. Modelling and Simulation in Science, Engineering and Technology (Birkhauser, Boston), 2008, in press. Bellomo, Chaplain, de Angelis Eds.

Upcoming: J Theor Biol, Nonlinearity, Cancer Res, **Cambridge University Press** and **Springer** books

- Diffuse interface **continuum** model of **multispecies** tumor growth and tumor-induced angiogenesis in two and three dimensions
- **Interfaces** are narrow transition layers that arise due to differential adhesive forces among the cell species. Accordingly, a continuum model of **adhesion** is introduced
- The model is thermodynamically consistent, is related to recently developed **mixture** models
- The model is well-posed and consists of **fourth-order nonlinear advection–reaction–diffusion equations** (of Cahn–Hilliard-type) for the cell species coupled with **reaction–diffusion equations** for the substrate components
- We demonstrate analytically and numerically that when the diffuse interface thickness tends to zero, the system reduces to a classical sharp interface model
- Using a new fully **adaptive** and **nonlinear multigrid/finite difference method**, the system is simulated efficiently
- **Our techniques now make large-scale three-dimensional simulations of tumors with complex morphologies computationally feasible**
- We investigate multispecies tumor **invasion**, tumor-induced **angiogenesis**, and focus on the **morphological instabilities** that may underlie invasive phenotypes

Alternative approach (finite elements)

→ X. Zheng, S. Wise, V. Cristini, Nonlinear simulation of tumor necrosis, neo-vascularization and tissue invasion via an adaptive finite-element/level-set method. *Bull Math Biol* 2005;67(2):211-59.

New Hot Paper in the field of Mathematics, Jul 06, Thomson-Scientific Essential Sci. Indicators.

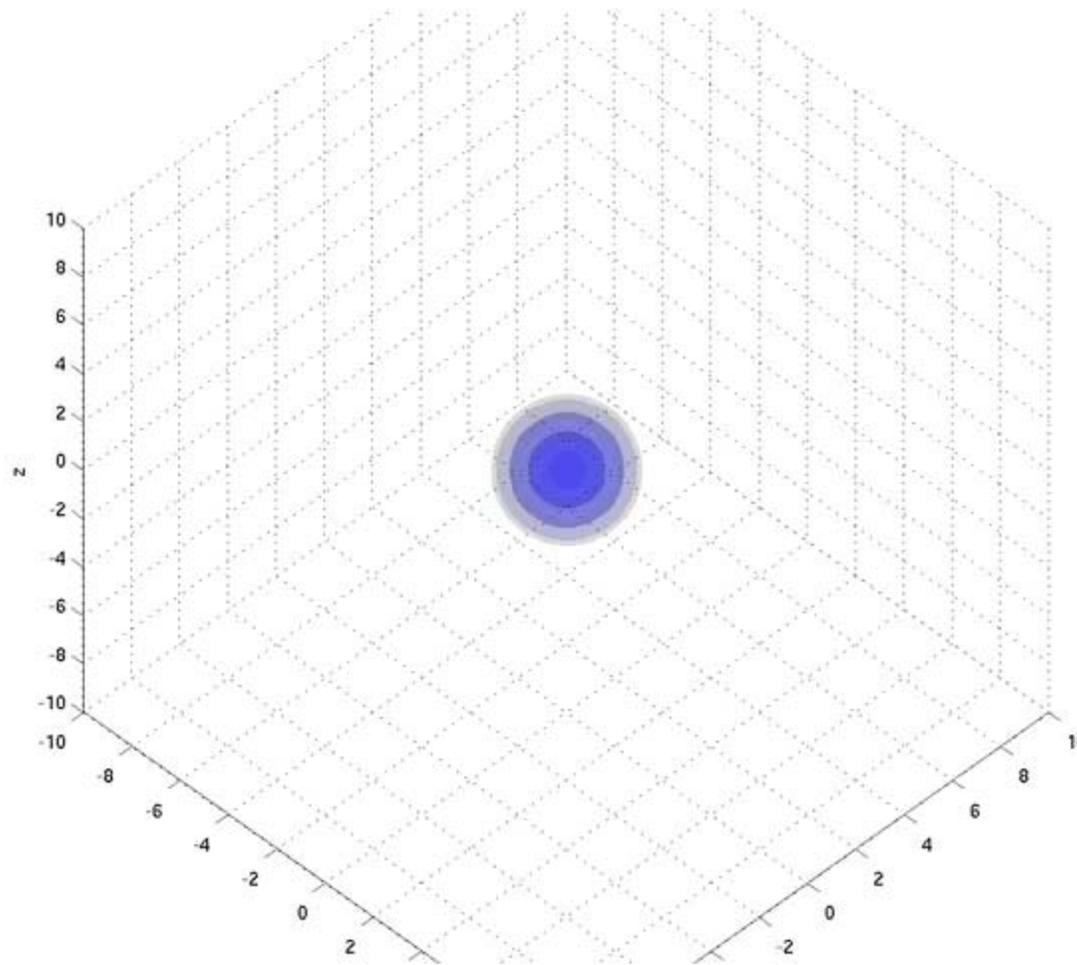
Front cover of Bulletin of Mathematical Biology 2006-2008

Math/Computational Continuum

Models

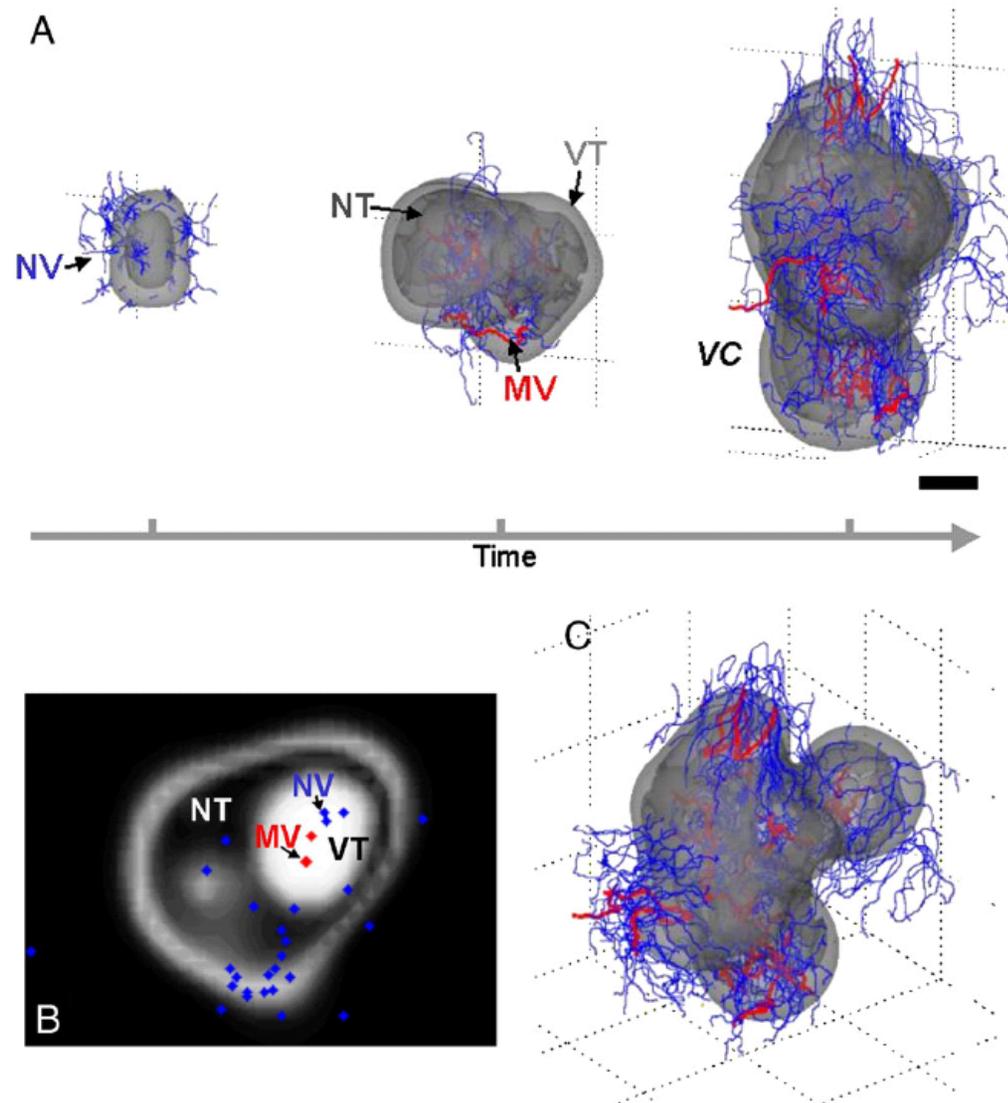
Funding: **NSF** (math), UC Discovery, Orqis Med, others

With **J Lowengrub** (UC Irvine) and others



Interplay of **transport (diffusion)** with proliferation, adhesion and vascularization leads to complex dynamic morphologies with important implications (see T Jackson/H Frieboes talk)

...3-D virtual tumors...



H. Frieboes, J. Lowengrub, S. Wise, X Zheng, E Bearer, V. Cristini, Computer simulation of glioma growth and morphology. *NeuroImage*; 37, S 1, 2007, S59-S70.

Predicting tumor growth and invasion

(T Jackson/H Frieboes)

Predicting growth of breast tumors

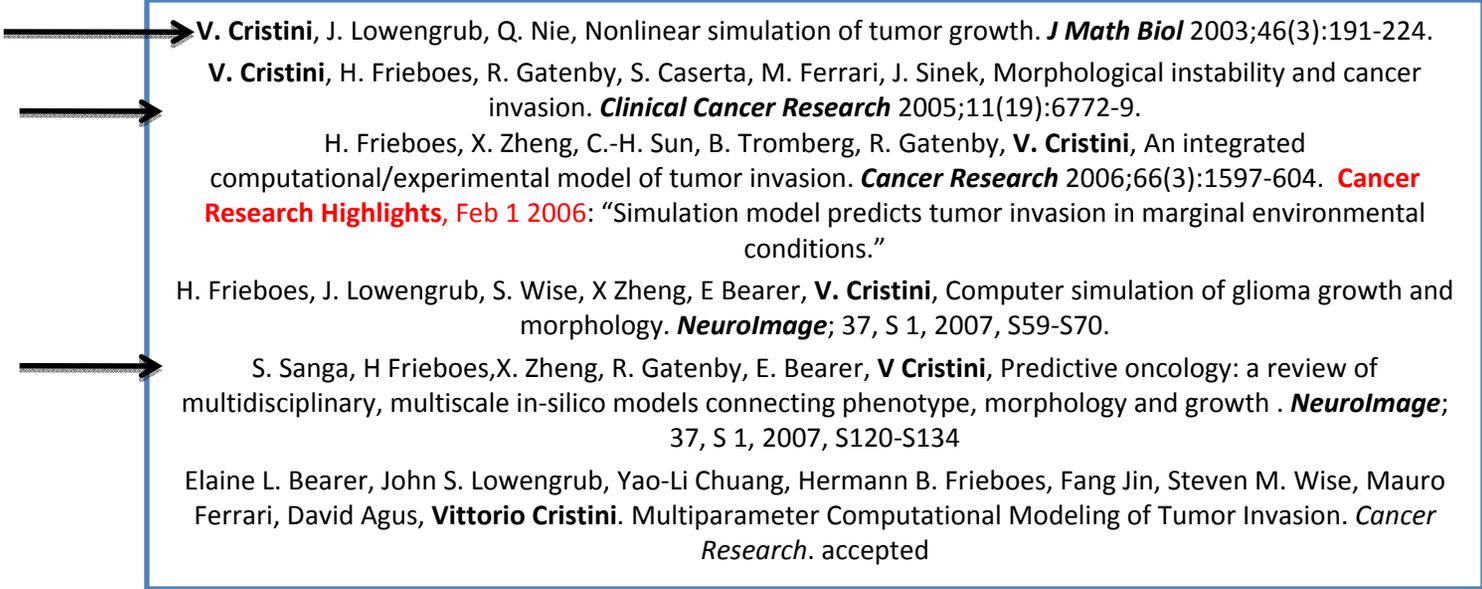
(M Edgerton)

Predicting tumor drug response

1. Predicting tumor growth and invasion

Funding: NSF (math), NIH, others

With E Bearer (Brown), J DeGroot (MD Anderson), D Agus (Cedars-Sinai), R Gatenby (Moffit), J Lowengrub (UC Irvine) and others



V. Cristini, J. Lowengrub, Q. Nie, Nonlinear simulation of tumor growth. *J Math Biol* 2003;46(3):191-224.

V. Cristini, H. Frieboes, R. Gatenby, S. Caserta, M. Ferrari, J. Sinek, Morphological instability and cancer invasion. *Clinical Cancer Research* 2005;11(19):6772-9.

H. Frieboes, X. Zheng, C.-H. Sun, B. Tromberg, R. Gatenby, V. Cristini, An integrated computational/experimental model of tumor invasion. *Cancer Research* 2006;66(3):1597-604. **Cancer Research Highlights, Feb 1 2006: "Simulation model predicts tumor invasion in marginal environmental conditions."**

H. Frieboes, J. Lowengrub, S. Wise, X Zheng, E Bearer, V. Cristini, Computer simulation of glioma growth and morphology. *NeuroImage*; 37, S 1, 2007, S59-S70.

S. Sanga, H Frieboes, X. Zheng, R. Gatenby, E. Bearer, V Cristini, Predictive oncology: a review of multidisciplinary, multiscale in-silico models connecting phenotype, morphology and growth . *NeuroImage*; 37, S 1, 2007, S120-S134

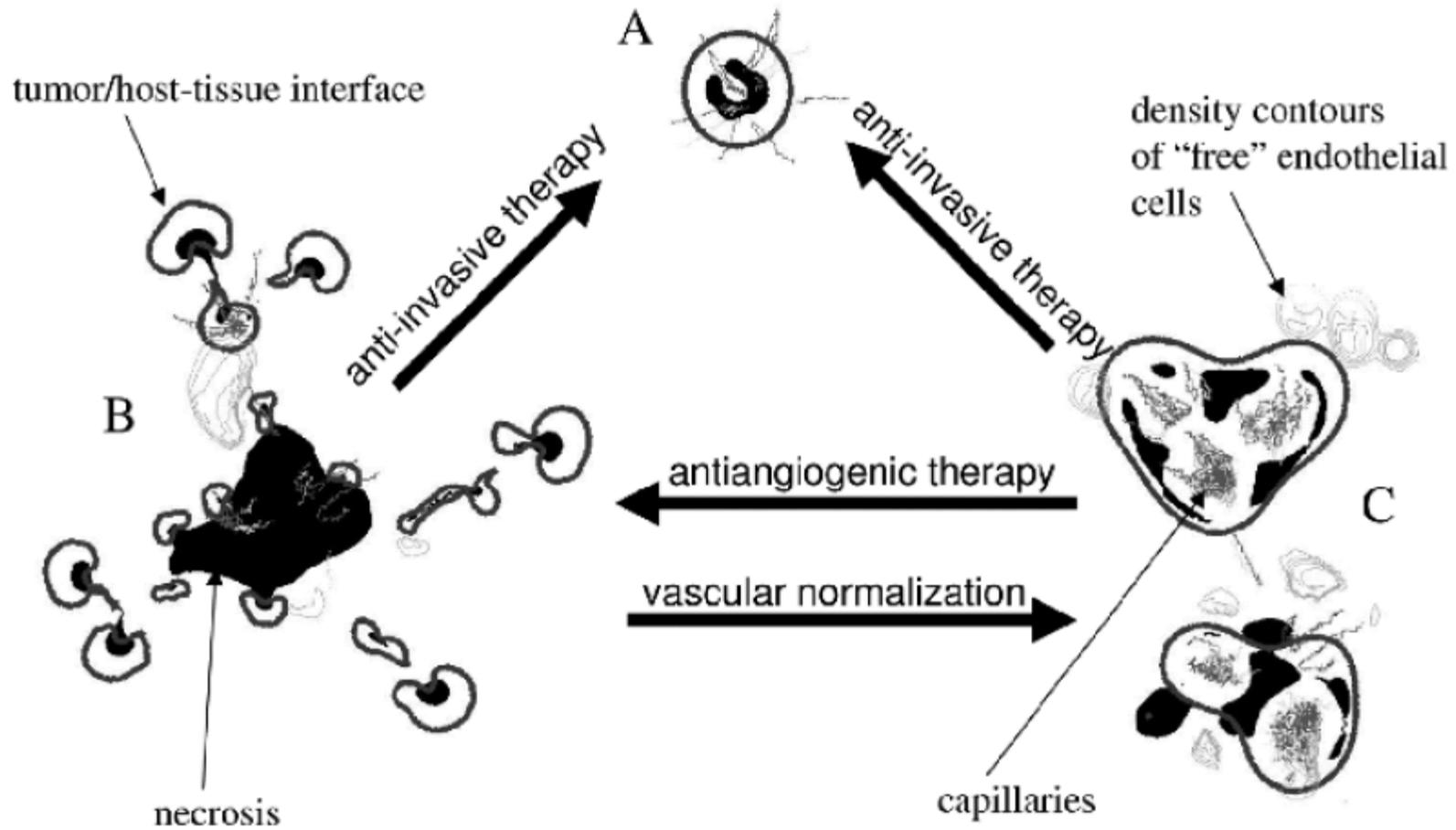
Elaine L. Bearer, John S. Lowengrub, Yao-Li Chuang, Hermann B. Frieboes, Fang Jin, Steven M. Wise, Mauro Ferrari, David Agus, **Vittorio Cristini**. Multiparameter Computational Modeling of Tumor Invasion. *Cancer Research*. accepted

Diffusion gradients of cell substrates drive **morphologic instability**, which is modulated by cell phenotype and leads to invasion by "fingering"

Experimental confirmation in vitro and in animal models

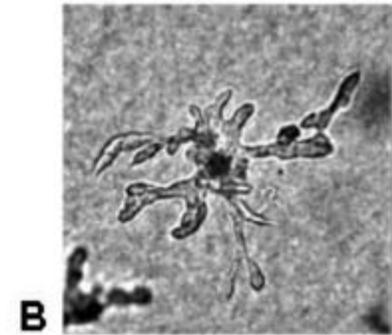
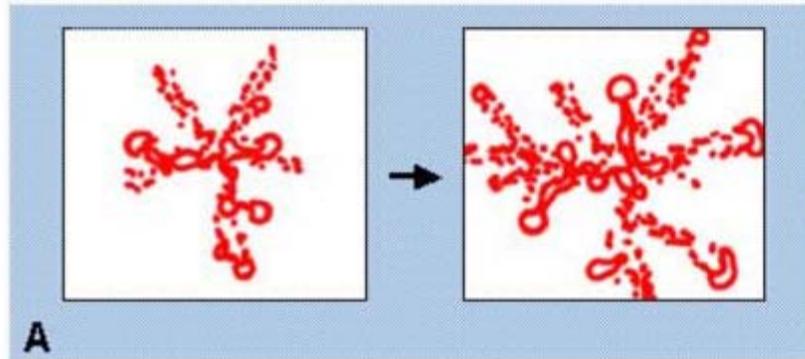
Confirmation from **patient clinical trials with anti-angiogenic therapy**

...Morphologic instability...

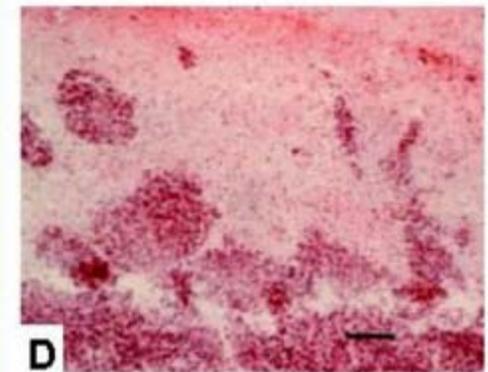
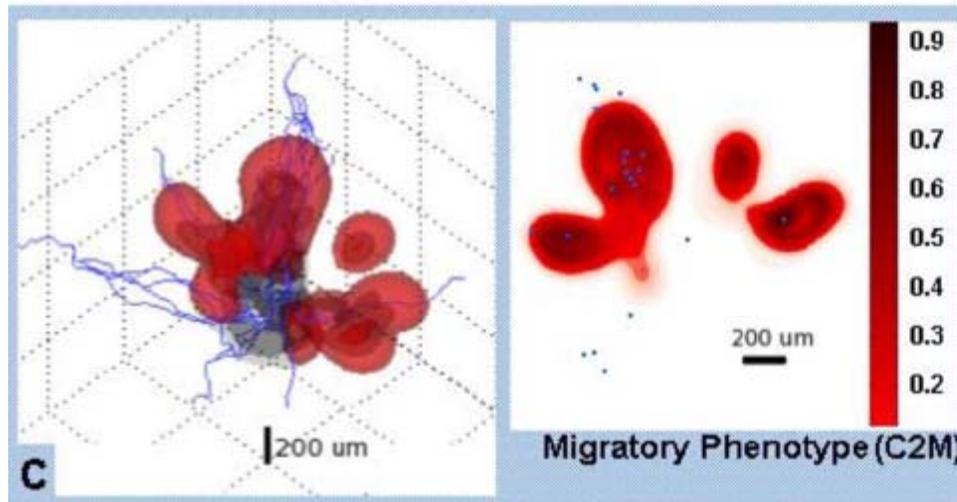


V. Cristini, H. Frieboes, R. Gatenby, S. Caserta, M. Ferrari, J. Sinek, Morphological instability and cancer invasion. *Clinical Cancer Research* 2005;11(19):6772-9.

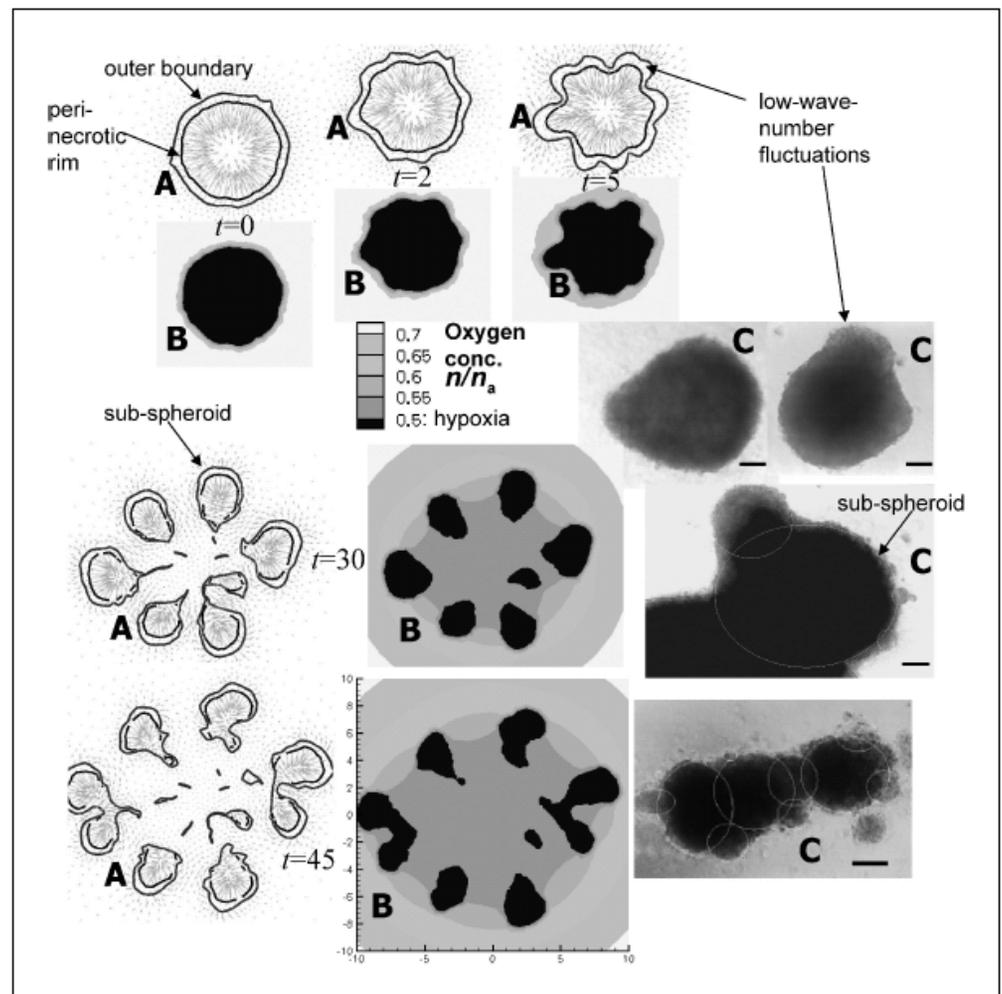
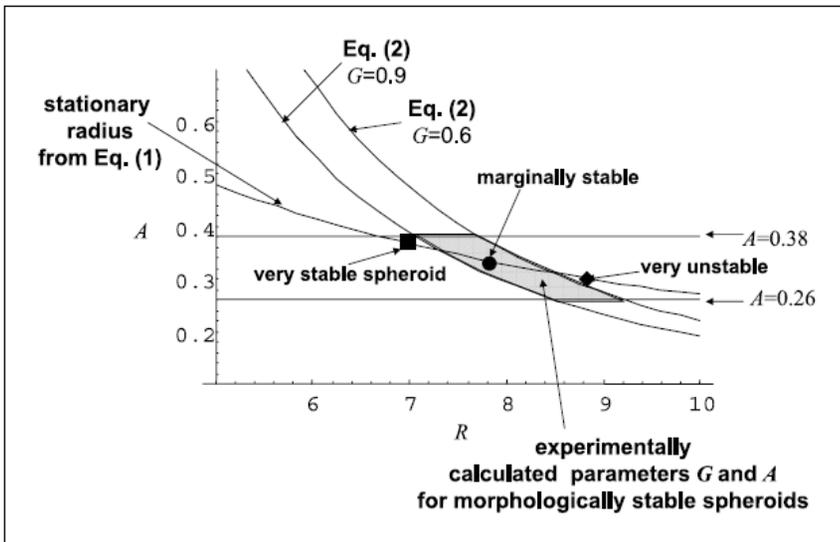
In vitro



In vivo

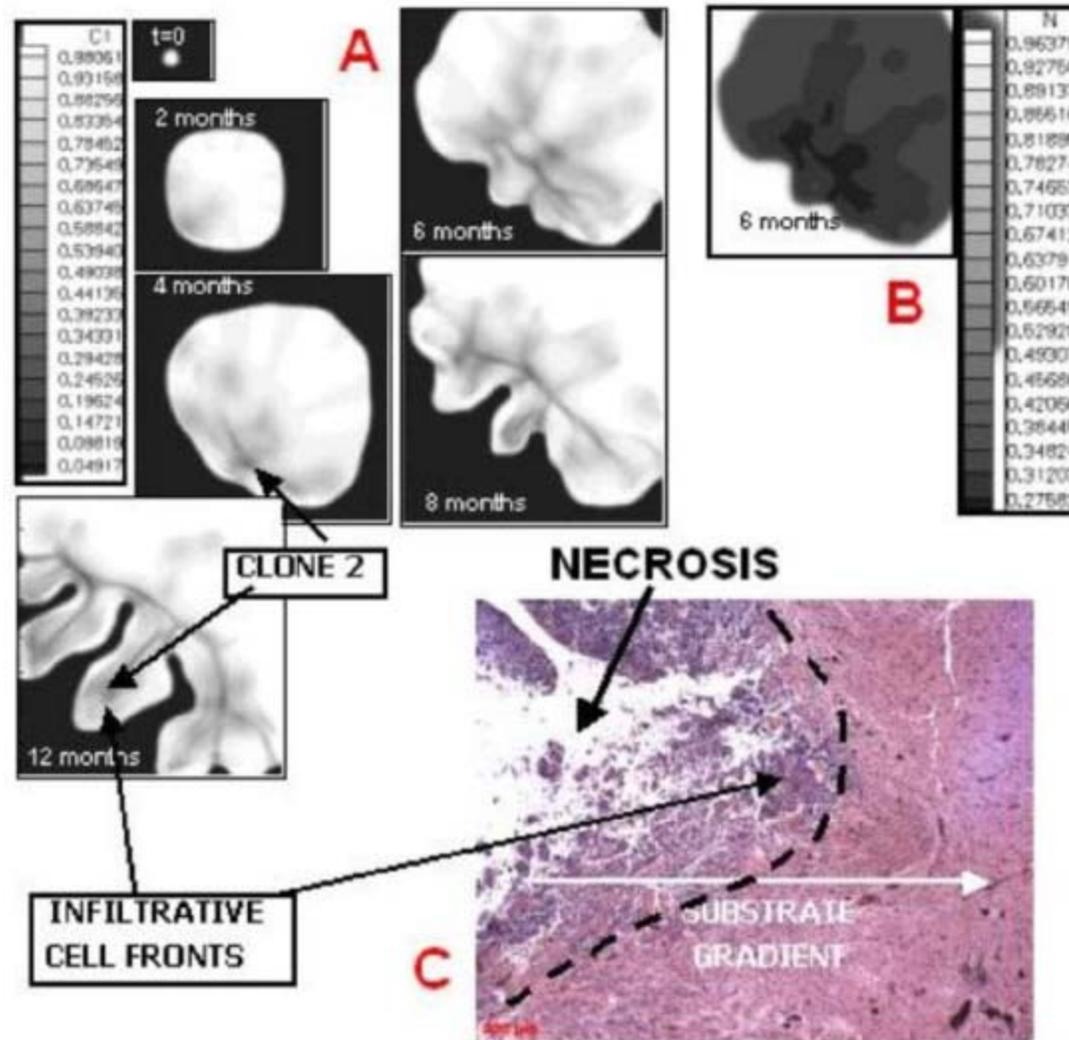


...a novel frontier for experimental oncology...



H. Frieboes, X. Zheng, C.-H. Sun, B. Tromberg, R. Gatenby, V. Cristini, An integrated computational/experimental model of tumor invasion. *Cancer Research* 2006;66(3):1597-604. **Cancer Research Highlights, Feb 1 2006:** "Simulation model predicts tumor invasion in marginal environmental conditions."

...clinical evidence...



Elaine L. Bearer, John S. Lowengrub, Yao-Li Chuang, Hermann B. Frieboes, Fang Jin, Steven M. Wise, Mauro Ferrari, David Agus, **Vittorio Cristini**. Multiparameter Computational Modeling of Tumor Invasion. *Cancer Research*. accepted

...more clinical evidence...

with J DeGroot MDACC

12/28/06

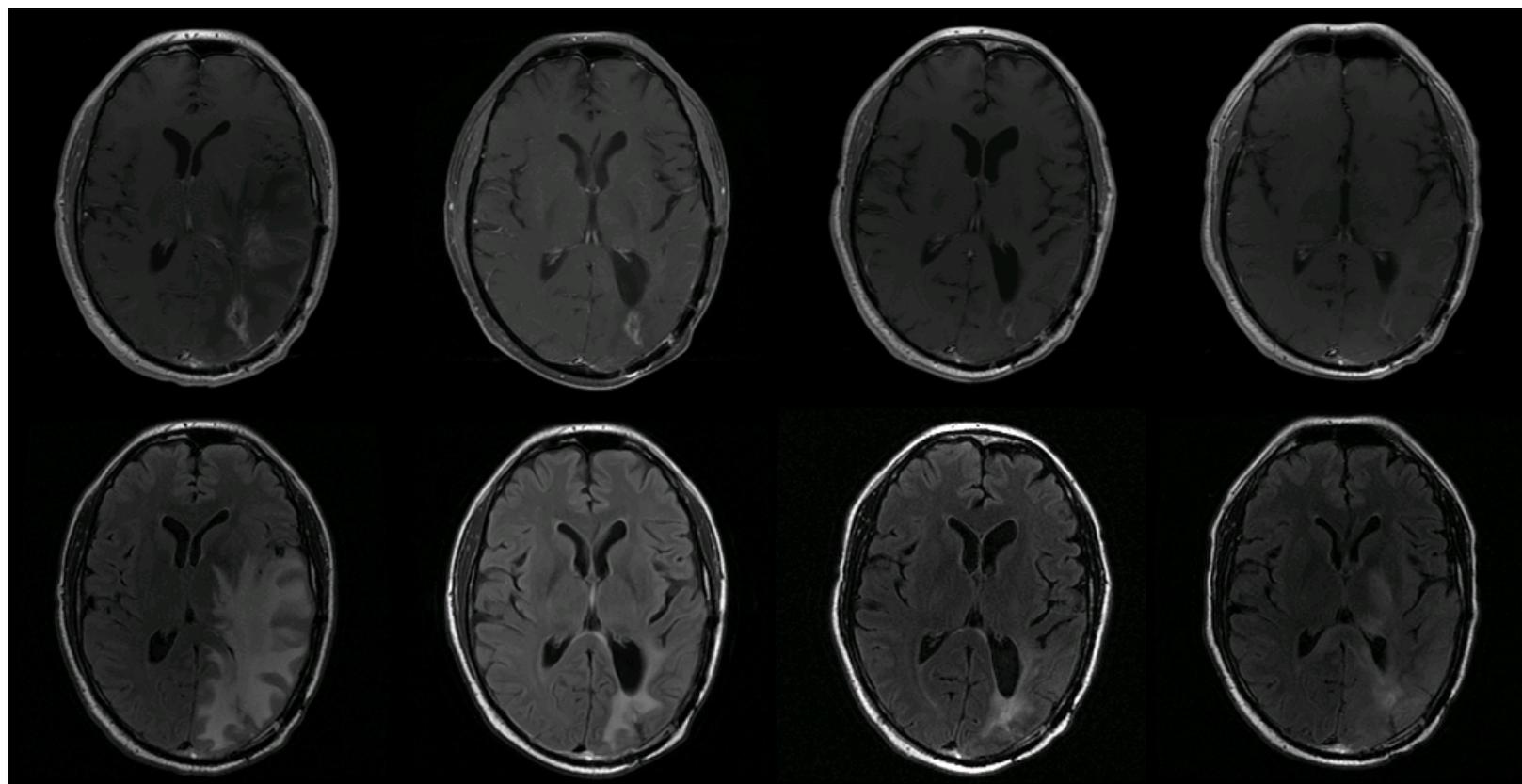
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T1 Post-Contrast
Enhancing tumor

Axial FLAIR
Non-enhancing tumor



bevacizumab

2. Predicting growth of breast tumors

Cell State:

T_i	cell type (tumor or epithelial)
S_i	cell state (Quiescent, Proliferative, Apoptotic, Motile, or Debris)
ϵ_i	surface e-cadherin expression (nondimensional)
I_i	surface integrin expression (nondimensional)
δ_i	cell deformability (nondimensional)
$1/\alpha_A$	mean time to enter apoptotic state
$1/\beta_A$	mean time to complete apoptosis
$1/\alpha_P$	mean time to enter proliferative state
$1/\beta_P$	mean cell cycle length

Cell Phenotype:

Cell Velocity:

$$\mathbf{v}_i = \frac{1}{\nu} \left(\underbrace{\alpha^{\text{cell}} \sum_{j \neq i}^N \epsilon_j \nabla \phi(R_{\text{cca}}, n_{\text{cca}}, \mathbf{x}_i - \mathbf{x}_j)}_{\text{cell-cell adhesion}} + \underbrace{\beta^{\text{cell}} \sum_{j \neq i}^N \frac{1}{\delta_j} \nabla \psi(r_j, n_{\text{ccr}}, \mathbf{x}_i - \mathbf{x}_j)}_{\text{cell-cell repulsion}} \right)$$

$$+ \underbrace{\alpha^{\text{BM}} I_i \nabla \phi(R_{\text{cba}}, n_{\text{cba}}, -d(\mathbf{x}_i) \mathbf{n})}_{\text{cell-BM adhesion}} + \underbrace{\beta^{\text{BM}} \nabla \psi(r_i, n_{\text{cbr}}, -d(\mathbf{x}_i) \mathbf{n})}_{\text{cell-BM repulsion}} + \mathbf{F}_{\text{locomotion}}$$

distance to duct wall → normal to duct wall

Interaction Potential Functions:

Adhesion:

$$\phi(R, n, \mathbf{x}) = \begin{cases} \frac{R}{n} \left(1 - \frac{|\mathbf{x}|}{R}\right)^n & \text{if } |\mathbf{x}| < R \\ 0 & \text{if } |\mathbf{x}| \geq R \end{cases}$$

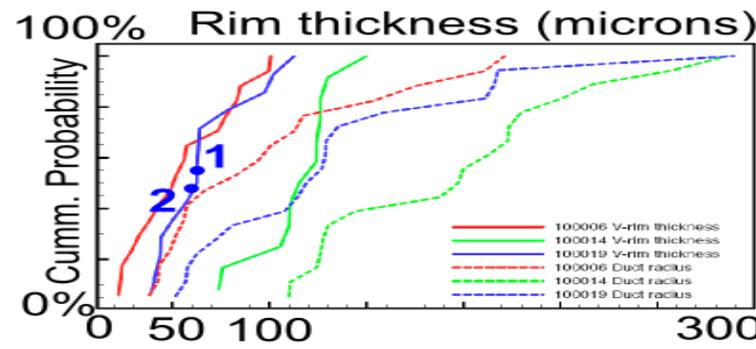
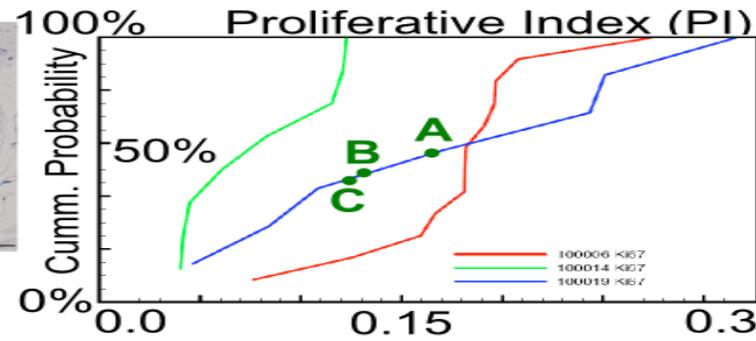
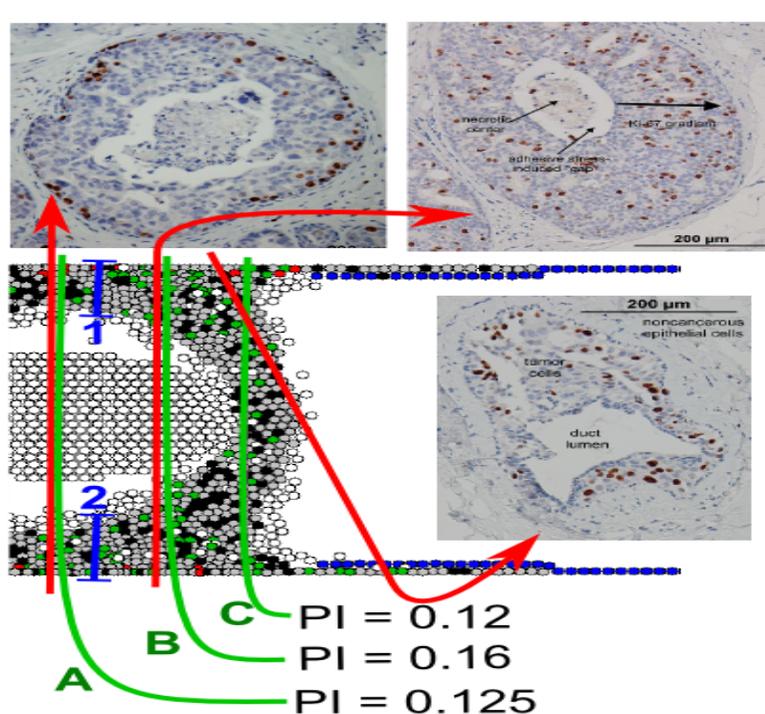
Repulsion:

$$\psi(R, n, \mathbf{x}) = \begin{cases} (|\mathbf{x}| - R) - \frac{R}{n} \left(\left(\frac{|\mathbf{x}|}{R}\right)^n - 1 \right) & \text{if } |\mathbf{x}| < R \\ 0 & \text{if } |\mathbf{x}| \geq R \end{cases}$$

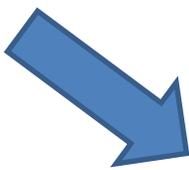
Project: Virtual cancer
 Funding: Cullen Trust for Health Care
 Collaborators: **M Edgerton, F Meric-Bernstam, W Yang and others** (MD Anderson)



Cell-agent discrete model (P Macklin)



Model calibration:



- $1/\beta_P$ Literature measurement of cell cycle time $[\tau]$
- $1/\beta_A$ Literature measurement of apoptosis completion time $[\tau]$
- S_i Assigned randomly to enforce IHC-measured apoptotic index (cleaved Caspase-3) and proliferative index (Ki-67)
- Cell-Cell Adhesion**
- R_{cca} histopathology measurement of max cell-cell adhesion distance
- $\langle r \rangle$ histopathology measurement of average equivalent cell radius
- n_{cca}, n_{ccr} Minimal values chosen such that correct qualitative cell behavior is achieved
- $\nu_{cell}/\nu, \beta_{cell}/\nu$ (1) histopathology measurements of mean cell density more than 20 microns from BM, and (2) enforcing time to cleave cells after end of proliferation
- ϵ_i Scaled relative to tumor e-cadherin IHC intensity in tumor and epithelial cells
- δ_i Set equal to 1.0 in current work
- Cell-BM Adhesion**
- R_{cba} histopathology measurement of max cell-BM adhesion distance
- n_{cba}, n_{cbr} Minimal values chosen such that correct qualitative cell behavior is achieved
- $\nu_{BM}/\nu, \beta_{BM}/\nu$ (1) histopathology measurements of mean cell density less than 20 microns from BM, and (2) enforcing "flattening" of cells against BM
- \mathcal{I}_i Scaled relative to tumor IHC indicators of integrin activity (e.g., motility), such as Her2/neu

Upscaling:

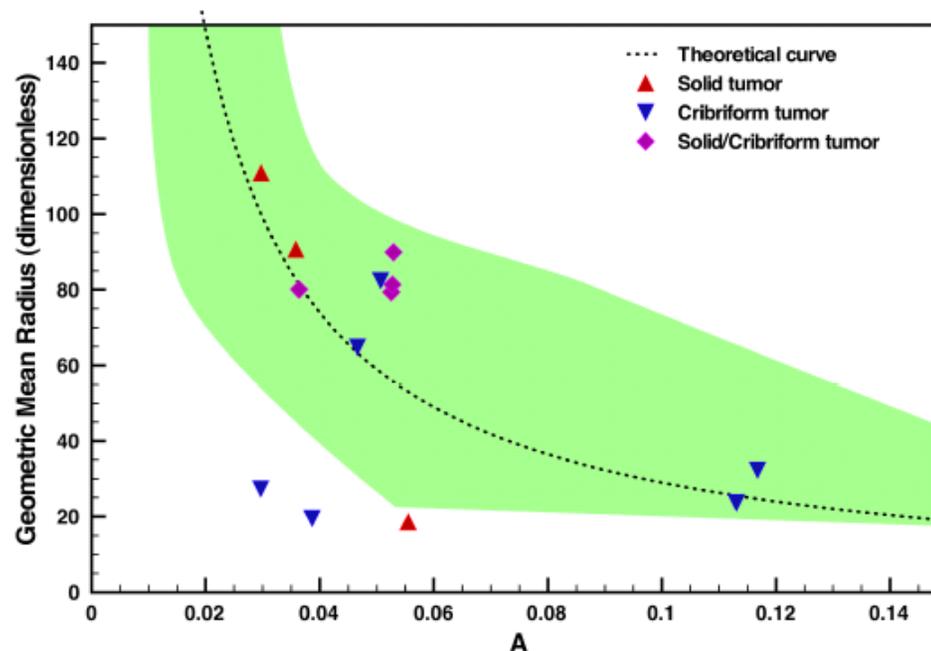
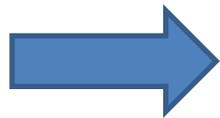
Input Parameters:

Parameter	Physical Meaning	Typical Value(s)
T_0	Characteristic time scale	18 hours
L_0	Characteristic length scale	50 – 300 μm
σ_B	Nutrient level in surrounding stroma	$\approx 100\%$
λ_A	Relative apoptosis rate with respect to the mitosis rate	0-1 (?)
M	Cell mobility	$\approx 100 \mu\text{m}^2/\text{min}$
α_{ep}	Cell-membrane adhesion parameter	
μ_0	Mitosis cutoff threshold	Corresponding to about 130% of the averaged tumor cell density
r_{duct}	Duct radius	50 – 100 μm
ε	Mixture interface thickness parameter	Corresponding to an interface $\geq 5 \mu\text{m}$

Output Variables:

Variable	Physical Meaning	Compared Physical Data	Significance
$\Phi(\mathbf{x}, t)$	Distribution of tumor cell volume fraction	Qualitatively: the tumor profiles in the histopathology images; Quantitatively: the estimated tumor growth rate	The profile of the tumor gives an estimate of the leading edge size, which can be used as an estimate for the surgical margin for breast-conserving surgery.
$\sigma(\mathbf{x}, t)$	Distribution of nutrient concentration	This auxiliary variable helps us to initiate the discrete simulations in the equation-free approach	

Accurate estimation of tissue-scale continuum parameters: “pathology-driven predictive modeling”



Accurate prediction of tumor size to improve surgical outcomes

Model is superior at reducing underestimated volumes with $p=0.02$

	Tumor Volumes Underestimated by Model		
Tumor Volumes Underestimated By Mammography	Yes (underestimated by model)	No (underestimated by model)	Total
Yes (underestimated by mammogram)	0	8	8 (67%)
No (not underestimated by mammogram)	1	3	4
Total	1 (<9%)	11	12

Data supports the hypothesis with a p values of 0.02 using McNemar's one-sided test (results have only 2% probability of having occurred by chance)

3. Predicting tumor drug response

Project: Biodistributions of silicon nanoparticles in breast cancer
Funding: NIH-BRP, DoD-TATRC
Collaborators: **M Ferrari** (UT Health Science Ctr)

Project: Biodistributions of gold nanoparticles and SWNT in head-and-neck cancer
Funding: DoD/ANH
Collaborators: **J Myers** (MD Anderson), **J Tour** (Rice)

Project: Breast and brain tumor response to chemotherapy and antiangiogenic therapy
Funding: Cullen Trust for Health Care, Komen foundation (prospective trials)
Collaborators: **F Symmans**, **M Edgerton**, **J DeGroot** and others (MD Anderson)

Project: Towards individualized breast cancer therapy: Leveraging molecular medicine with multi-stage vector technology.
Funding: DOD/BCRP Innovator Award
Collaborators: **M Ferrari** (UT Health Science Ctr)

J Sinek, H Frieboes, X Zheng, **V Cristini**, Two-dimensional chemotherapy simulations demonstrate fundamental transport and tumor response limitations involving nanoparticles. *Biomed Microdev* 2004;6(4):297-309.

S. Sanga, J. Sinek, H. Frieboes, M. Ferrari, J. Fruehauf, **V. Cristini**, Mathematical modeling of cancer progression and response to chemotherapy: towards the development of a multiscale computer simulator. *Expert Rev Anticancer Therapy* 2006;6(10):1361-76.

→ J Sinek, S Sanga, X Zheng, M. Ferrari, **V Cristini**, Predicting drug PKPD and tumor response using computer simulations. *J Math Biol*. DOI 10.1007/s00285-008-0214-y; 2008.

→ H. B. Frieboes, Mary E. Edgerton, J. P. Fruehauf, F. R. A. J. Rose, L. K. Worrall, R. A. Gatenby, M. Ferrari and **V. Cristini**. Prediction of drug response in breast cancer using integrative experimental/computational modeling. *Cancer Res*. In press

H Frieboes, P Decuzzi, J Sinek, M Ferrari, **V Cristini**, Computational Modeling of Tumor Biobarriers: Implications for Delivery of Nano-based Therapeutics. In: Mingjun Zhang and Ning Xi (Eds.). *Nanomedicine: A Systems Engineering Approach*, Pan Stanford Publishing -- an affiliated company of the World Scientific Publishers, 2008.

S. Sanga, H. Frieboes, J. Sinek, **V. Cristini**, A multiscale approach for computational modeling of biobarriers to cancer chemotherapy via nanotechnology. In: *Cancer Nanotechnology*, eds: T. Webster, H. S. Nalwa; American Scientific Publishers 2006; Ch. 10, pp. 1-21

J. Sinek, H. Frieboes, B. Sivaraman, S. Sanga, **V. Cristini**, Mathematical and computational modeling: Towards the development and application of nanodevices for drug delivery. In: Series: Nanotechnologies for the Life Sciences; Vol. 4: Nanodevices for the Life Sciences, ed: C Kumar; pp. 29-66; Wiley-VCH 2006

H. Frieboes, J. Sinek, O. Nalcioglu, J. Fruehauf, **V. Cristini**, Nanotechnology in cancer drug therapy: a biocomputational approach. In: *BioMEMS and Biomedical Nanotechnology* 2006; Vol. 1: Prospectus, Biological and Biomedical Nanotechnology, eds: A.P. Lee, L.J. Lee; Springer-Verlag; Ch. 15, pp. 435-460

Diffusion gradients of **both** drug and substrates introduce physiologic resistance greatly diminishing drug effect

Substrate, and not drug gradients, play major role

Nanocarriers subject to same **fundamental transport limitations**

...experimental evidence

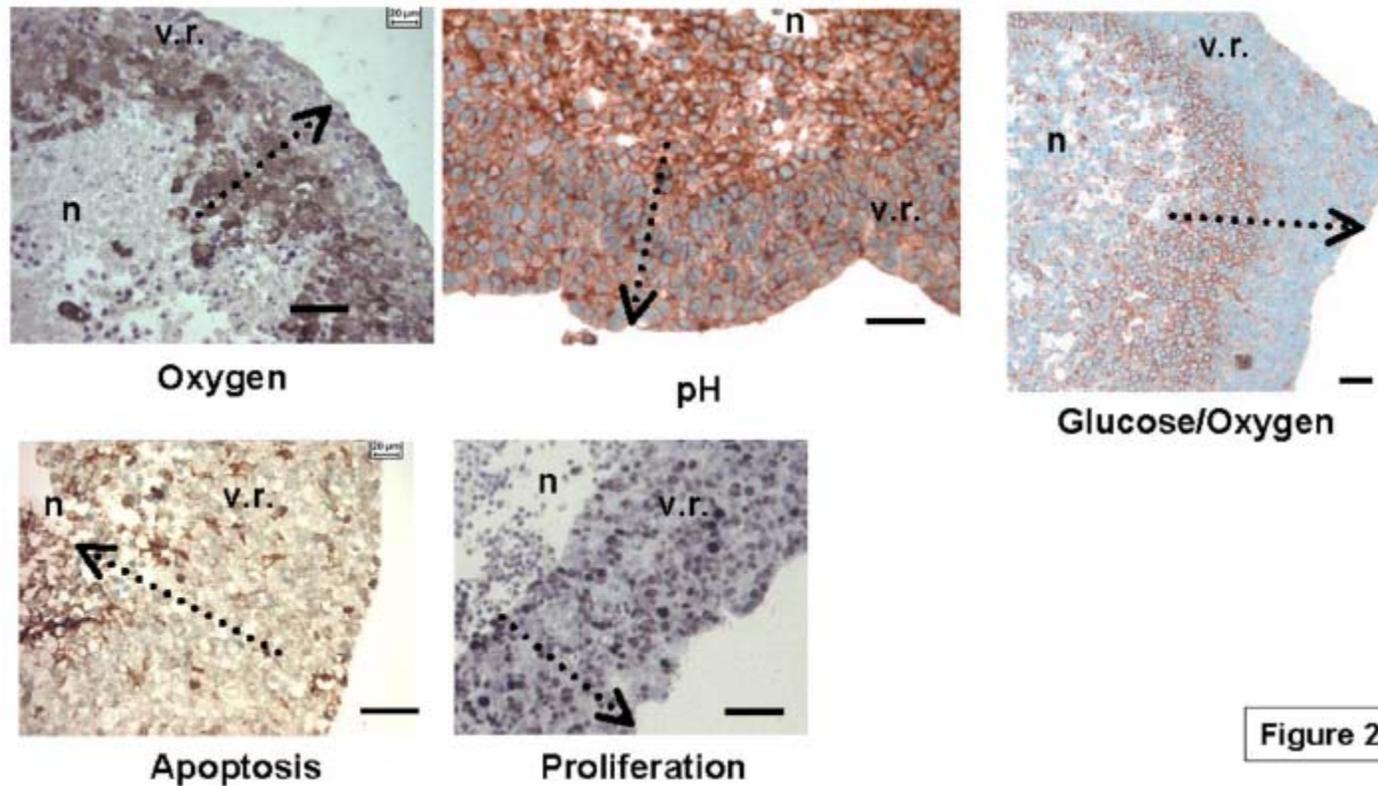
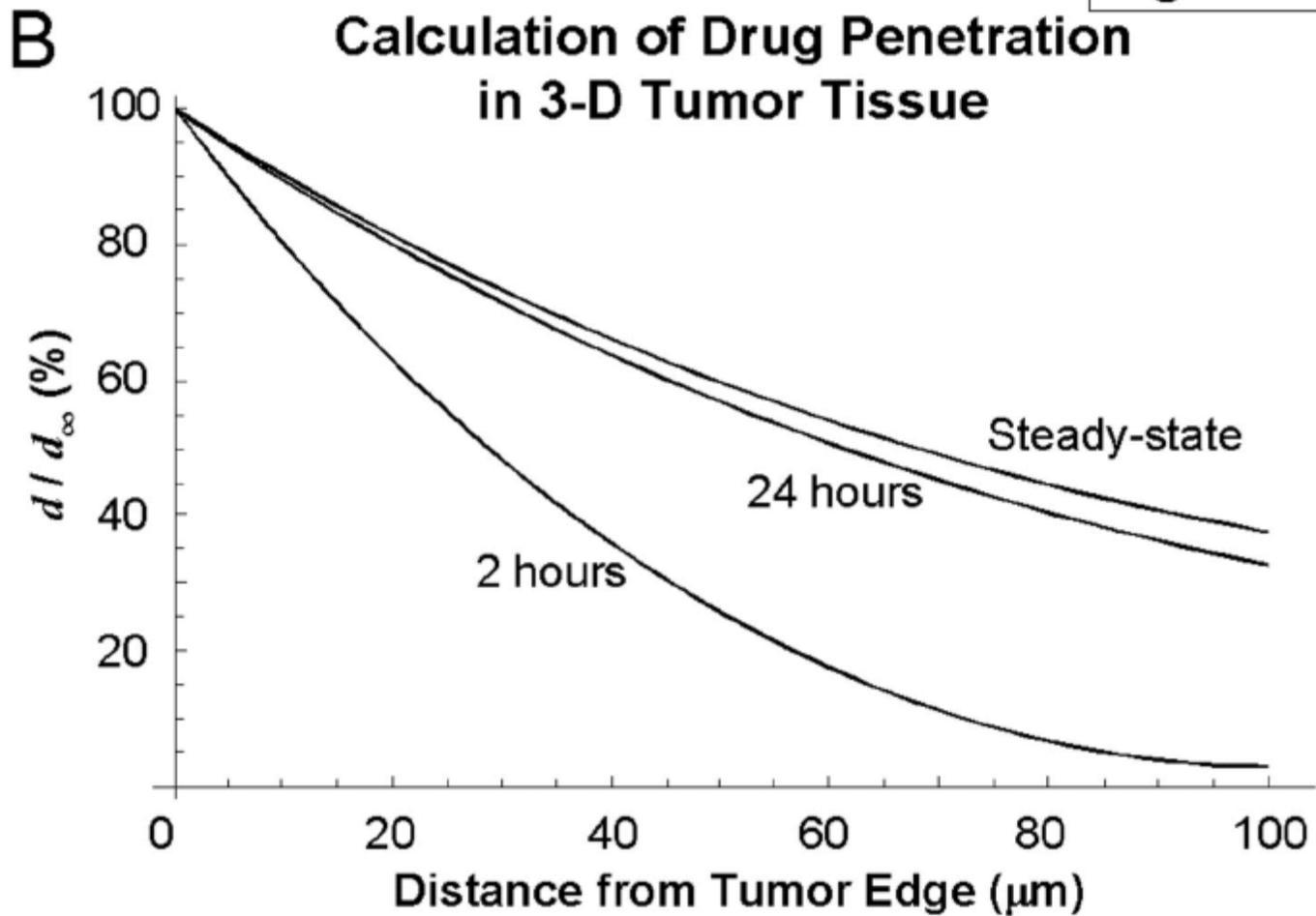


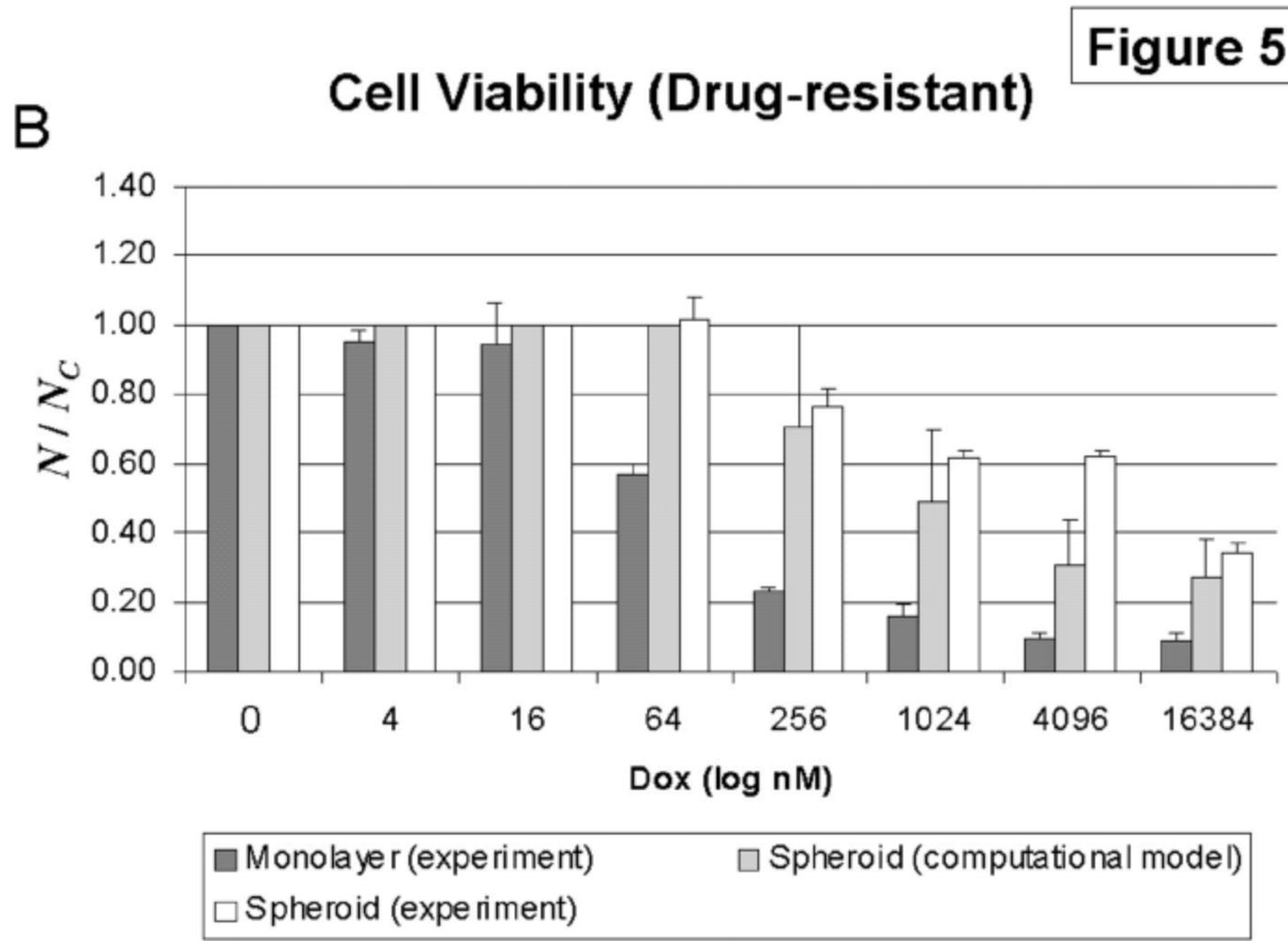
Figure 2

H. B. Friebes, Mary E. Edgerton, J. P. Fruehauf, F. R. A. J. Rose, L. K. Worrall, R. A. Gatenby, M. Ferrari and **V. Cristini**. Prediction of drug response in breast cancer using integrative experimental/computational modeling. *Cancer Res.* In press

Figure 3



...cytotoxicity experiments...



...model calibration...

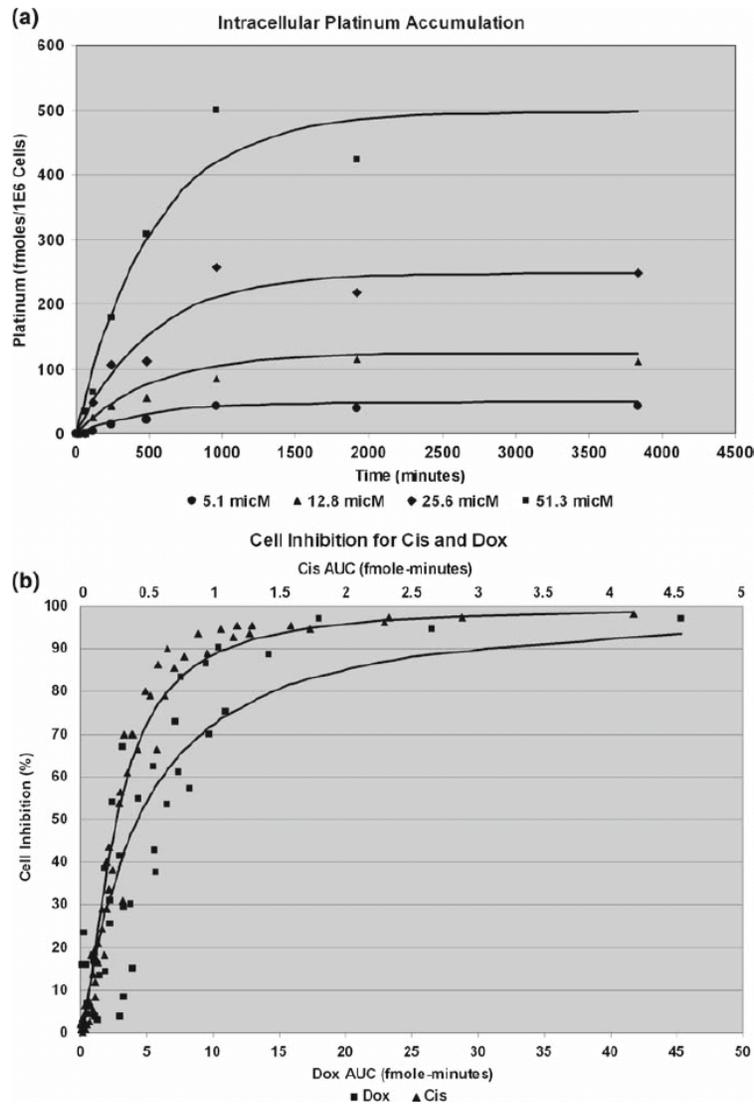


Table 1 A complete summary of baseline pharmacokinetics and pharmacodynamics parameters

Parameter	Description	Baseline Value	
		Dox	Cis
V_c	Cell volume (fL cell ⁻¹)	520	520
ρ	Cell density (cells mL ⁻¹)	1.0E9	1.0E9
F	Interstitial fraction	0.48	0.48
D_n	Nutrient/ECM diffusivity ($\mu\text{m}^2 \text{min}^{-1}$)	60E3	60E3
D_s	Drug/ECM diffusivity ($\mu\text{m}^2 \text{min}^{-1}$)	1.0E3	30E3
k_n	Nutrient metabolism (min ⁻¹)	24	24
k_{12}	Drug uptake (min ⁻¹)	5.40	0.054
k_{21}	Drug efflux (min ⁻¹)	5.40	1.56E-3
k_{23}	Drug-DNA binding (min ⁻¹)	8.02E5	3.82E-4
k_{32}	Drug-DNA release (min ⁻¹)	1.80E3	0.0
k_3	Drug-DNA repair (min ⁻¹)	0.0	0.015
k_{24}	Lysosomal sequestration (min ⁻¹)	10.0	0.0
k_{42}	Lysosomal release (min ⁻¹)	0.07	0.0
s_m	Drug-DNA capacity (fmole)	1.00	∞
A	Phenomenological PD parameter	0.188	7.75
m	Phenomenological PD parameter	1.14	1.58
p	Nutrient effect parameter	0.4	0.0

Tumor growth and angiogenesis parameters can be found in [82]

J Sinek, S Sanga, X Zheng, M. Ferrari, **V Cristini**,
 Predicting drug PKPD and tumor response using
 computer simulations. ***J Math Biol.*** DOI
 10.1007/s00285-008-0214-y; 2008.

...effect of transport (diffusion) barriers...

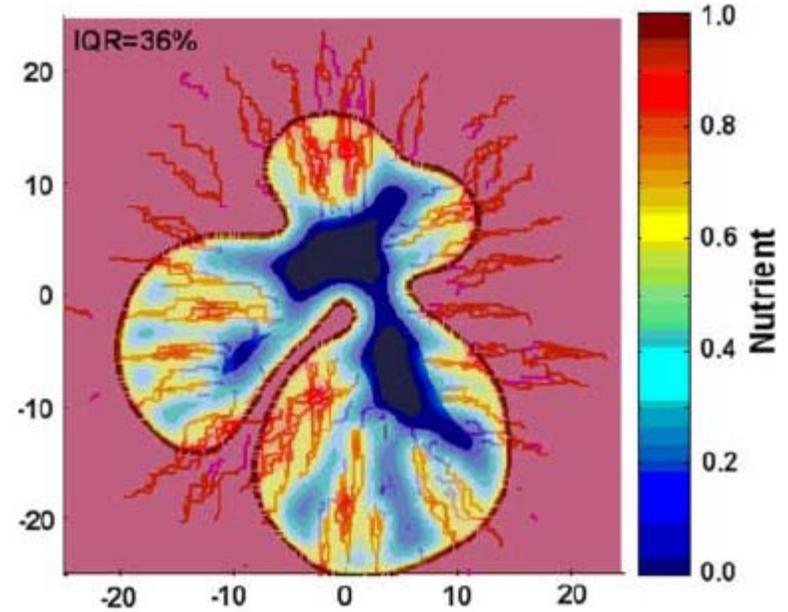
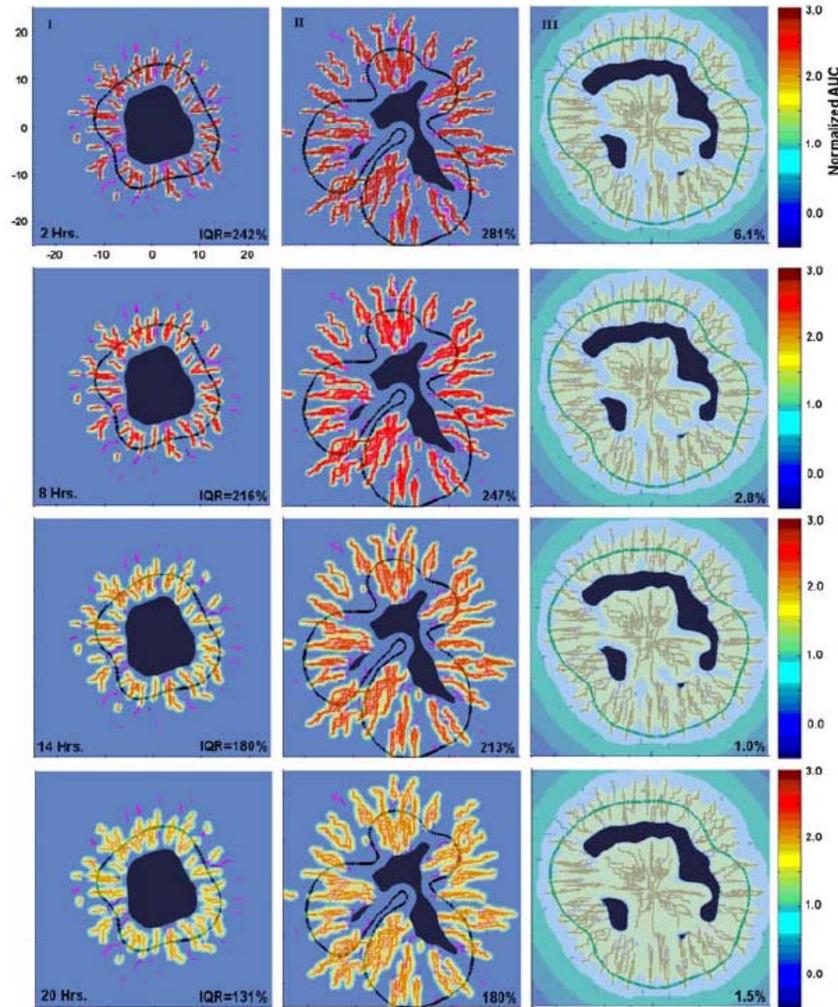
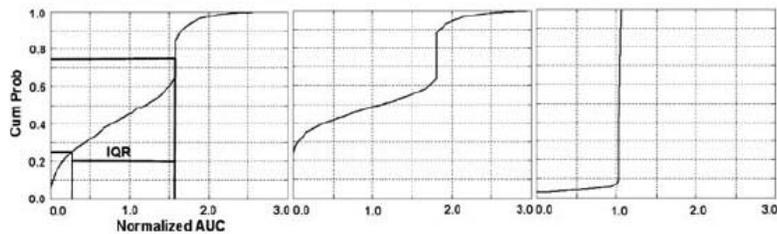


Table 2 Mean \pm SD of the IC_{50} and the logs of their ratios with respect to monolayer treatments for experiments to investigate the impact of drug and nutrient heterogeneity

Nutrient effect	$IC_{50,mono}(\mu M)$	$IC_{50}(\mu M)$	$\log(IC_{50}/IC_{50,mono})$
Doxorubicin baseline			
Off	0.175	0.482 ± 0.163	0.424 ± 0.138 ($*p < 0.05$)
On	0.175	1.34 ± 0.874	0.830 ± 0.261 ($*p < 0.05$)
Doxorubicin with penetration therapy			
Off	0.175	0.197 ± 0.0172	0.0511 ± 0.0371 ($p > 0.05$)
On	0.175	0.371 ± 0.0356	0.325 ± 0.0407 ($*p < 0.05$)
Cisplatin baseline			
N/A	7.05	7.14 ± 0.0757	0.00529 ± 0.00462 ($p > 0.05$)



$IC_{50,mono}$ is the IC_{50} of baseline cells in monolayer. At the 5% significance level using a one-tailed t test, the average log ratio for cisplatin does not exceed 0. On the other hand, in three of the four experiments with doxorubicin, they do. Paired one-tailed t tests show that the average log IC_{50} ratios for doxorubicin with the nutrient effect are greater than that without regardless of penetration therapy

...towards predictive drug response models

